Role of Bisphenol A in Human Diseases. An Update

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Abstract- Bisphenol A (BPA) is an industrial chemical that has been present in many hard plastic bottles and metal-based food and beverage cans since the 1960s. The US Food and Drug Administration (FDA), the European Food Safety Authority (EPSA) and numerous government agencies worldwide for use in food contact application. Because bisphenol A is used in so many common products that we use every day—such as baby bottles, reusable water bottles, microwaveable containers, and the protective coating inside most food and beverage cans—most people in developed countries are exposed almost continuously to some level of bisphenol A. The safety threshold set by the EPA was based on decades-old data. On the basis of results from recent studies using novel approaches to test for subtle effects, both the National Toxicology Program at the National Institutes of Health and FDA have some concern about the potential effects of BPA on the brain, behavior, and prostate gland in fetuses, infants, and young children. Like many chemicals, BPA is found in the blood and urine of virtually every American tested by the Centers for Disease Control and Prevention. Devised opinions among scientists about the exposure to BPA and health implications are going on, some arguing that its effect on health in negligible, but some has proved with studies about its effect on variety of disorders. This paper is therefore an attempt to review the recent concepts on the exposure of BPA in various disorders.

Index Terms- Bisphenol A (BPA), CDC, EPSA, CVD

I. Introduction

Despite the fact that more than 5000 safety-related studies have been published on bisphenol A (BPA), there seems to be no resolution of the apparently deadlocked controversy as to whether exposure of the general population to BPA causes adverse effects due to its estrogenicity. BisphenolA (BPA) is an industrial chemical that has been present in many hard plastic bottles and metal-based food and beverage cans since the 1960s. It has been used for decades to make toys, food containers, medical equipmentand many common products such as water bottles, food storage containers, airplane and automobile components, sports safety equipment and medical devices. Because bisphenol A is used in so many common products that we use every day—such as baby bottles, reusable water bottles, microwaveable containers, and the protective coating inside most food and beverage cans—most people in developed countries are exposed almost continuously to some level of bisphenol A.

Of late potential health effects of BPA have been detected in almost all conceivable type of human diseases. Numerous studies have shown its adverse effect on human health and the FDA recent statement “that it is virtually impossible for most people to experience as unsafe level of BPA exposure in their daily life”.

II. Bisphenol A in General Health & Disease

That the current TDI for BPA is adequately justified and that the available evidence indicates that BPA exposure represents no noteworthy risk to the health of the human population, including newborns and babies (1).

Higher BPA exposure is associated with general and central obesity in the general adult population of the United States. Reverse causation is of concern due to the cross-sectional nature of this study; longitudinal studies are needed to clarify the direction of the association (2).

Higher BPA exposure, reflected in higher urinary concentrations of BPA, may be associated with avoidable morbidity in the community-dwelling adult population (3).

Using a sensitive and quantitative competitive enzyme-linked immunosorbent assay, BPA was found to migrate from polycarbonate water bottles at rates ranging from 0.20 to 0.79 ng per hour. At room temperature the migration of BPA was independent of whether or not the bottle had been previously used. Exposure to boiling water (100°C) increased the rate of BPA migration by up to 55-fold. The estrogenic bioactivity of the BPA-like immune reactivity released into the water samples was confirmed using an *in vitro* assay of rapid estrogen-signaling and neurotoxicity in developing cerebellar neurons. The amounts of BPA found to migrate from polycarbonate drinking bottles should be considered as a contributing source to the total “EDC-burden” to which some individuals are exposed (4).

No detectable BPA was found in the extracts obtained under FDA's most severe default testing condition using a method sensitive to 5 parts per billion (ppb) in the food stimulants. Using these data, along with FDA's conventional procedure for estimating potential dietary exposure using food simulating migration data, the potential dietary exposure to bisphenol A from use of polycarbonate resins was determined to be less than 0.25 ppb (5).

Penetration of the skin depends on the conditions. Extractability experiments did not enable us to conclude whether BPA passes through the skin, but indicated that it can enter the skin to such a depth that it can no longer be washed off. If this BPA ends up in the human metabolism, exposure of a person repeatedly touching thermal printer paper for 10 h/day, such as at a cash register, could reach 71 ìg/day, which is 42 times less than the present tolerable daily intake (TDI). However, if more than just the finger pads contact the BPA-containing paper or a hand cream enhances permeability of the skin, this margin might be smaller (6).

III. Bisphenol A in Dialysis

Bisphenol A [BPA, 2,2-bis(4-hydoxyphenyl)propane], an industrial chemical used in the production of polycarbonate, epoxide resin, and polyarylate, is considered to be an endocrine-disrupting chemical. BPA may be present in some hollow-fiber dialyzers used in hemodialysis. Among renal disease patients who had not undergone hemodialysis, the serum BPA concentration increased as the renal function deteriorated, showing a significant negative association. Since accumulation of BPA could affect the endocrine or metabolic system of the human body, it is important to perform further investigations on dialysis patients (7).

In in vitro experiments, BPA was detected in the effluents of the PS-C, PS-D and EVAL hemodialyzers. In in vivo experiments, BPA was detected in whole blood samples from hemodialysis patients treated with the PS-D hemodialyzer (mean value, 0.77 ppb)(8).

IV. Bisphenol in renal disease

The estrogenic endocrine-disrupting substance bisphenol A (BPA) is extensively used as a starting material for a variety of consumer plastic products including dialyzer materials. In the randomized controlled study, the plasma BPA concentrations were highly elevated compared with healthy controls (range 9.1 ± 4.5-12.0 ± 6.0 ng/mL vs. $\leq 0.2 \pm 0.1$ ng/mL; $P < 0.001$), but no change of the plasma levels was observed during hemodialysis. Dialyzers are one additional source of BPA, but differences in the elutable BPA content are not associated with a significant effect on BPA plasma levels in Western European maintenance dialysis patients. Due to high protein binding, the removal of BPA by hemodialysis is limited (9)

Urinary excretion of triclosan, and possibly BPA, decreased with decreasing renal function. The associations might differ by age or sex. Further studies are necessary to replicate our results and understand the mechanism (10).

V. Bisphenol and heart disease

Recent animal studies have suggested that BPA exposure may have a role in several mechanisms involved in the development of cardiovascular disease (CVD), including weight gain, insulin resistance, thyroid dysfunction, endothelial dysfunction, and oxidative stress. A significant, positive association between increasing levels of urinary BPA and PAD before and after adjusting for confounders. The multivariable-adjusted odds ratio for PAD associated with the highest versus lowest tertile of urinary BPA was 2.69 (95% confidence interval: 1.02, 7.09; *p*-trend = 0.01).Urinary BPA levels were significantly associated with PAD, independent of traditional CVD risk factors (11).

Recent studies have suggested that cardiovascular diseases are associated with the BPA exposure. Urinary BPA was associated negatively with the root mean square of successive differences for heart rate and positively with blood pressure (12).

BisphenolA (BPA) is an estrogenizing endocrine disruptor compound of concern. Continual exposure to BPA impacts cardiac structure/function, protein expression, and epigenetic DNA methylation marks in males and females (13).

Associations between higher BPA exposure (reflected in higher urinary concentrations) and incident CAD during >10 years of follow-up showed trends similar to previously reported cross-sectional findings in the more highly exposed NHANES respondents. Further work is needed to accurately estimate the prospective exposure-response curve and to establish the underlying mechanisms (14).

Higher BPA exposure, reflected in higher urinary concentrations of BPA, is consistently associated with reported heart disease in the general adult population of the USA. Studies to clarify the mechanisms of these associations are urgently needed (15).

There is evidence of associations between raised urinary bisphenol A (uBPA) and increased incidence of reported cardiovascular diagnoses. BPA exposure was higher in those with severe coronary artery stenoses compared to those with no vessel disease (16).

VI. BPA and cancer

BisphenolA (BPA) is the principal constituent of baby bottles, reusable water bottles, metal cans, and plastic food containers. BPA exerts estrogen-like activity by interacting with the classical estrogen receptors (ERα and ERβ) and through the G protein-coupled receptor (GPR30/GPER). In this regard, recent studies have shown that GPER was involved in the proliferative effects induced by BPA in both normal and tumor cells. GPER is required for growth effects and migration stimulated by BPA in both cell types. GPER is involved in the biological action elicited by BPA in breast cancer cells and CAFs. Hence, GPER-mediated signaling should be included among the transduction mechanisms through which BPA may stimulate cancer progression (17).

The first scientific paper reporting on the synthesis of BisphenolA (BPA) was published in 1905 based on the research conducted by Thomas Z incke in the University of Marburg in Germany. 1953- Polycarbonate plastic developed and commercial production of BPA and polycarbonate begin. BPA, highly present in natural world and considered as a model of environmental estrogen action complexity, promotes human cancer cell proliferation via ERα-dependent signal transduction pathways (18).

BisphenolA (BPA) has been suspected as a potential risk factor for breast cancer. In age-matched subjects ($N = 152$), there were some associations between BPA levels and risks of breast

cancer, such as age at first birth and null parity. However, there were no significant differences in blood BPA levels between the cases and the controls ($P = 0.42$) (19).

BPA response profile was significantly associated with breast tumors characterized by high histologic grade ($P < 0.001$) and large tumor size ($P = 0.002$), resulting in decreased recurrence-free patient survival ($P < 0.001$) (20).

After androgen deprivation, BPA enhanced both cellular proliferation rates and tumor growth. These effects were mediated, at least in part, through androgen receptor activity, as prostate-specific antigen levels rose with accelerated kinetics in BPA-exposed animals. Thus, at levels relevant to human exposure, BPA can modulate tumor cell growth and advance biochemical recurrence in tumors expressing the AR-*T877A*mutation (21).

VII. Bisphenol A and menopause

BishphenolA (BPA) is a representative endocrine disruptor and is also known as a xenoestrogen. There was no statistical significance between serum BPA concentration and clinical variables related to bone metabolism. To clarify the effect of BPA on bone metabolism, further large scaled and high risk group investigation may be needed (22).

VIII. Bisphenol A and metabolic syndrome

Urinary BPA levels are positively associated with MetS, in a representative sample of US adults and independent of traditional risk factors for MetS. Future, prospective studies are needed to confirm our findings (23).

IX. Bisphenol A and diabetis mellitus

BisphenolA (BPA) is a widely used chemical in the manufacture of polycarbonate plastics and epoxy resins. Recent animal studies have suggested that BPA exposure may have a role in the development of weight gain, insulin resistance, pancreatic endocrine dysfunction, thyroid hormone disruption, and several other mechanisms involved in the development of diabetes. Urinary BPA levels are found to be associated with diabetes mellitus independent of traditional diabetes risk factors. Future prospective studies are needed to confirm or disprove this finding (24).

A positive association between higher levels of urinary BPA and prediabetes, independent of potential confounders including body mass index, alcohol intake, blood pressure and serum cholesterol levels. Higher urinary BPA levels are found to be associated with prediabetes independent of traditional diabetes risk factors. Future prospective studies are needed to confirm or disprove this finding (25).

Long-term BPA exposure at a dose three times higher than the tolerable daily intake of 50 µg/kg, appeared to accelerate spontaneous insulitis and diabetes development in NOD mice (26).

Although higher urinary BPA was associated with elevated HbA1c and T2DM in the pooled analysis, it was driven by data from only one NHANES cycle. Additional studies, especially of a longitudinal design with repeated BPA measurements, are needed to further elucidate the association between BPA and T2DM (27).

X. Bisphenol A and drinking water

BPA is a ubiquitous contaminant in surface, tap and bottled mineral water. However, exposure to BPA from drinking water is very low and is less than 0.01% of the tolerable daily intake (TDI) (28).

Significant amounts of BPA leached from bottle containers into thewater. Long storage of bottled water under direct sunlight should be avoided to reduce the risk of human exposure to BPA (29).

BPA in drinking water represents a minor component of overall human exposure, and compared with the lowest available oral toxicity benchmark of 16 µg/kg-bw/day (includes an uncertainty factor of 300) gives margins of safety >1100. Human biomonitoring data indicate that ingestion of drinking water represents <2.8% of the total intake of BPA (30).

XI. Bisphenol A and Endocrine functions

Similarities exist between the effects of exposure to BPA and other related chemicals with schizophrenia. These similarities can be observed in 11 broad categories of abnormality: physical development, brain anatomy, cellular anatomy, hormone function, neurotransmitters and receptors, proteins and factors, processes and substances, immunology, sexual development, social behaviors or physiological responses, and other behaviors. Some of these similarities are sexually dimorphic and support theories that sexual dimorphisms may be important to schizophrenia pathogenesis (31).

Higher BPA exposure may be associated with endocrine changes in men. The mechanisms involved in the observed cross-sectional association with total testosterone concentrations need to be clarified (32).

XII. Bisphenol A and liver disease

High dose of BPA (50 mg/kg) significantly increased the biochemical levels of ALT, ALP and total bilirubin. BPA effect on the activity of antioxidant genes was confirmed by real time PCR in which the expression levels of these genes in liver tissue were significantly decrease compared to control. Data from this study demonstrate that BPA generate ROS and reduce the antioxidant gene expression that causes hepatotoxicity (33).

XIII. Bisphenol A and reproductive

A dose–response relationship was observed with an increasing level of cumulative BPA exposure associated with a higher risk of sexual dysfunction. Furthermore, compared with the unexposed workers, BPA-exposed workers reported significantly higher frequencies of reduced sexual function within 1 year of employment in the BPA-exposed factories.Our findings provide the first evidence that exposure to BPA in the

workplace could have an adverse effect on male sexual dysfunction (34).

Exposure to high doses of BPA during the period of brain sexual differentiation altered the hypothalamic–pituitary–gonadal axis in female Sprague-Dawley rats. These results have the potential to link neonatal exposure to high doses of BPA in rats with the development of polycystic ovarian syndrome. Studies of doses and routes of administration more consistent with human exposures are needed to determine the relevance of these findings to human health (35).

XIV. Conclusion

Contrary to older concept that BPA is harmless, recent findings have linked BPA to variety of disease. However, definitive studies have not been undertaken to elucidate the mechanism of action in inducing various disorders. Future studies should be based on this aspect. Further a simple, reliable and cost effective methodology should be developed compared to expensive HPLC technique which is being used at present. BPA measurement should be brought to diagnostic usefulness.

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